Janssen Research & Development

Statistical Analysis Plan

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rilematovir (JNJ-53718678) in Adult Outpatients with Respiratory Syncytial Virus (RSV) Infection who are at High Risk for RSV-related Disease Progression

PRIMROSE

Effects of Rilematovir in Adult Outpatients with RSV Infection who are at High Risk for RSV-related Disease Progression

Protocol 53718678RSV2008; Phase 2b

JNJ-53718678 (rilematovir)

Status: Approved
Date: 24 May 2022
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document No.: EDMS-RIM-436373, 1.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	24 May 2022	Not Applicable	Initial release

1. INTRODUCTION

On 14-Apr-2022, the Sponsor took the strategic decision to discontinue the development of rilematovir (JNJ-53718678) and therefore to terminate the 53718678RSV2008 (PRIMROSE) study and substudies. At that time, there was no ongoing participant in the main study, and 5 subjects had been enrolled and had completed the Day 35 study visit or discontinued earlier. Although a stable version of the Statistical Analysis Plan (SAP) for the main study was available (EDMS-RIM-436373 V0.10), it was decided to simplify and to reduce the statistical outputs to individual patient profiles because data of only 5 randomized participants were collected in the main study. Therefore, no summary statistics across participants will be produced, and data will be reported as a listing generated for each participant (patient profile).

For the PRIMROSE Biosensor substudy, no SAP will be produced because no participants were enrolled in the substudy and therefore no data were collected.

This SAP covers the final analysis of the main study. It contains identification of variables that will be included in patient profiles and reported for the clinical study report (CSR), and definitions of derived variables for the PRIMROSE main study. The SAP is to be interpreted in conjunction with the protocol.

Due to the small number of participants no pharmacokinetic (PK) or pharmacokinetic/pharmacodynamics (PK/PD) analysis will be performed, and only the listing of observed plasma levels of rilematovir will be reported in the CSR.

Rilematovir is an investigational respiratory syncytial virus (RSV) specific fusion inhibitor belonging to the indole chemical class and was under development for the treatment of RSV infection in adults and pediatric population.

1.1. Objectives and Endpoints

Given the small number of enrolled participants, no analyses will be performed to evaluate the study objectives listed in Table 2. Only individual patient profiles will be provided.

Table 2: Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate efficacy of rilematovir compared to placebo with respect to the time to resolution of respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) symptoms.	• Time to resolution of RSV LRTD symptoms (ie, cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by the participant using the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™ Symptom Scale). Definition of resolution in participants without pre-existing respiratory symptoms: - *All LRTD symptoms in the RiiQ™ Symptom Scale[a] scored as 'None' (score = 0) or 'Mild'*

Table 2: Objectives and endpoints

Objectives	Endpoints
	(score =1) for at least 24 hours. Definition of resolution in participants with pre-existing respiratory symptoms: - *Pre-existing symptoms that were worse at baseline should have improved at least 1 point on the RiiQ™ Symptom Scale from baseline for at least 24 hours; and* - *Pre-existing symptoms that were not worse at baseline should have not worsened from baseline severity for at least 24 hours; and* - *Symptoms that were not pre-existing at baseline should be scored as 'None' (score = 0) or 'Mild' (score =1) on the RiiQ™ Symptom Scale for at least 24 hours*
Secondary	
• To evaluate the effect of rilematovir compared to placebo with respect to the incidence of post-baseline RSV-related complications.	• Proportion of participants with post-baseline complications (ie, RSV-related pulmonary and extrapulmonary complications). - **Pulmonary complications:** primary viral pneumonia, bronchitis, respiratory failure, secondary bacterial pneumonia, and exacerbations of underlying chronic pulmonary diseases (such as chronic obstructive pulmonary disease [COPD] and asthma). - **Extrapulmonary complications**: cardiovascular and cerebrovascular disease events, congestive heart failure (CHF) or exacerbation of underlying CHF, acute exacerbation of chronic kidney disease, severe dehydration, decompensation of previously controlled diabetes mellitus, and other airway infections (eg, sinusitis).
• To evaluate the effect of rilematovir as compared to placebo on medical resource utilization (MRU) with respect to respiratory therapeutic interventions associated with RSV-related disease progression.	• Proportion of participants with new antibiotic use, or new or increased use in bronchodilator/nebulizer, systemic corticosteroids, or home oxygen supplementation.
• To evaluate the effect of rilematovir as compared to placebo on MRU with respect to medically attended visits associated with	• Proportion of participants with unscheduled outpatient clinic visits, emergency room visits or

Table 2: Objectives and endpoints

Objectives	Endpoints
RSV-related disease progression.	hospitalization for respiratory infection.
• To evaluate the effect of rilematovir as compared to placebo on the overall RSV-related disease progression.	• Proportion of participants meeting a composite endpoint of either developing RSV-related complications (pulmonary & extra pulmonary) and/or needing RSV-related medical attendance.
• To evaluate the safety and tolerability of rilematovir.	• Safety and tolerability, as assessed by AEs, clinical laboratory testing, electrocardiograms (ECGs), physical examination, and vital signs.
• To evaluate the effect of rilematovir compared to placebo on the clinical course of RSV infection.	• Change from baseline over time in severity of the RSV LRTD symptoms as assessed by the participant using the RiiQ™ Symptom Scale. • Time to resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue) as assessed by the participant using the RiiQ™ Symptom Scale. • Time to resolution of the overall RSV symptoms (upper respiratory tract disease [URTD: sore throat and nasal congestion], LRTD, and 2 systemic symptoms [feeling feverish and fatigue]) as assessed by the participant using the RiiQ™ Symptom Scale. • Time to resolution of all RSV symptoms as assessed by the participant using the RiiQ™ Symptom Scale. • Time to resolution of each separate RSV LRTD symptom as assessed by the participant using the RiiQ™ Symptom Scale. Definition of resolution in participants without pre-existing respiratory symptoms: • *All LRTD symptoms in the RiiQ™ Symptom Scale[a] scored as 'None' (score = 0) or 'Mild' (score =1) for at least 24 hours.* Definition of resolution in participants with pre-existing respiratory symptoms: • *Pre-existing symptoms that were worse at baseline should have improved at least 1 point on the RiiQ™ Symptom Scale from baseline for at least 24 hours; and* • *Pre-existing symptoms that were not worse at baseline should have not worsened from baseline severity for at least 24 hours, and,* • *Symptoms that were not pre-existing at baseline should be scored as 'None' (score = 0) or 'Mild'*

Table 2: Objectives and endpoints

Objectives	Endpoints
	(score =1) on the RiiQ™ Symptom Scale for at least 24 hours. • Time to return to pre-existing health (status) for all RSV symptoms as assessed by the participant using the RiiQ™ Symptom Scale. • Time to resolution of respiratory infection symptoms as assessed by the participant using the Patient Global Impression of RSV Severity (PGI-S) Scale. • Time to improvement in RSV disease as assessed by the participant using the Patient Global Impression of Change (PGI-C) Scale.
• To evaluate the effect of rilematovir compared to placebo on Health-Related Quality of Life (HRQOL).	• Change from baseline over time for the HRQOL as assessed by participants using the EQ-5D-5L and RiiQ™ Impact Scales. • Time to return to usual health as assessed by the participant using the 'Adult RSV Return to Usual Health' question. • Time to return to usual activities as assessed by the participant using the 'Adult RSV Return to Usual Activities' question. • Time to no or mild impact of RSV-related disease on daily activities, emotions, and social relationships as assessed by the participant using the RiiQ™ Impact Scales.
• To evaluate the antiviral effect of rilematovir as measured by RSV viral load in bilateral nasal mid-turbinate swab samples by quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay.	• RSV viral load area under the curve from immediately prior to first dose of study intervention (baseline) through Day 3, Day 5, Day 8. • Change from baseline over time in RSV viral load. • Proportion of participants with undetectable RSV viral load at each time point that a swab is planned to be collected.
• To evaluate the emergence of mutations in the viral genome potentially associated with resistance to rilematovir.	• Post-baseline sequence changes in the RSV F gene.
• To evaluate the PK of rilematovir.	• Pharmacokinetic parameters of rilematovir (ie, C_{trough}, C_{max}, and AUC_{0-12h}).
• To evaluate the impact of rilematovir compared to placebo on MRU.	• Number and type of medical encounters. • Shift in any care setting (e.g. from no assistance

Table 2: Objectives and endpoints

Objectives	Endpoints
	to use of skilled home nurse or assisted home living). • Proportion of participants requiring hospitalization for respiratory or other reasons and duration of hospitalization (total days length of stay, including incidence and where feasible duration by wards, eg, intensive care unit [ICU]). • Incidence and duration of treatment-emergent use of antibiotics. • Incidence and duration of treatment-emergent new use or increased dose of systemic or inhaled corticosteroids and bronchodilators. • Proportion of participants with new or increased use of oxygen therapy. • Duration of oxygen supplementation. • Duration of selected post-baseline emergent (after start of study intervention) MRU.
Exploratory	
• To explore the relationship between antiviral activity and the primary and key secondary clinical outcomes.	• Respiratory syncytial virus viral load-based endpoints and primary and key secondary clinical course endpoints.
• To explore the impact of rilematovir compared to placebo on RSV disease-related progression and complications.	• The proportion of participants progressing to ICU including the need for mechanical ventilation (yes or no). • All-cause mortality up to Day 35.
• To evaluate the impact of rilematovir compared to placebo on the clinical course of disease using the Clinician Symptom Score (CSS).	• Change from baseline over time in the CSS as assessed by a Clinician Questionnaire.
• To explore the relationship between PK of rilematovir and PD (selected antiviral activity, clinical outcomes, and safety parameters).	• Pharmacokinetic/PD analysis of plasma concentration-time data of rilematovir and selected clinical outcomes, antiviral activity, and safety parameters.
• To explore the impact of rilematovir compared to placebo on hours missed from work (by all members of the participant's household, including the participant, if employed).	• Hours missed from work due to the participant's RSV infection by all members of the participant's household, including the participant, if employed.
[a] The RiiQ™ Symptom scale is a four-item scale (0: no symptoms, 1: mild symptoms, 2: moderate symptoms, 3: severe symptoms).	

1.2. Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy, safety, and tolerability of rilematovir at a dose of 250 mg twice daily administered for 7 days in outpatient adults (≥18 to ≤85 years of age) who have at least moderate RSV disease (LRTD) due to RSV infection, and who are at high risk of RSV-related disease progression. Moderate RSV disease is defined as having at least any 2 of the symptoms of LRTD (cough, wheeze, coughing up phlegm, short of breath), at least one of which must be scored as at least 'moderate' if the symptoms did not pre-exist before RSV onset, and/or at least one of which must be scored worse than usual if the symptoms pre-existed as determined by the participant's ratings of the RiiQ™ Symptom Scale and the Pre-Existing Symptom Questionnaire in the electronic Patient Report Outcome (ePRO) device.

A target of 180 participants who are at high risk for RSV-related disease progression is planned in this study. Participants are randomized in a 2:1 ratio (active:placebo) with approximately 120 participants planned in the rilematovir group and approximately 60 participants in the placebo group. Randomization to study intervention treatment should occur within 72 hours after onset of any of the RSV symptoms or worsening of pre-existing symptoms.

High-risk condition(s) for RSV-related disease progression is defined as:

- Presence of any of the underlying high-risk comorbid cardiopulmonary conditions (COPD, asthma, or CHF) AND/OR
- ≥65 years of age (elderly participants).

Randomization is stratified by high-risk (<65 years of age with underlying high-risk comorbid cardiopulmonary conditions [COPD, asthma, or CHF] versus ≥65 years of age without underlying comorbid cardiopulmonary conditions versus ≥65 years of age with underlying comorbid cardiopulmonary conditions), and time since symptom onset (≤48 hours versus >48-72 hours).

The study population should consist of at least 50% of participants with randomization ≤48 hours since onset of RSV symptoms.

Participants who meet all eligibility criteria are randomized in a 2:1 ratio to receive 1 of the following 2 treatments:

- Treatment A: rilematovir 250 mg twice daily for 7 days (n = 120)

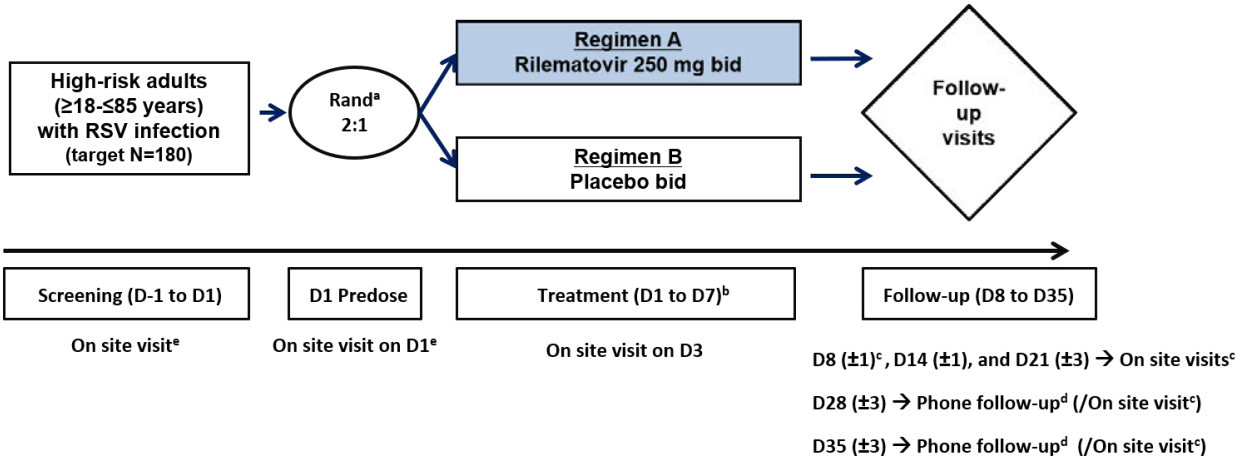
  with dose reduction to 125 mg twice daily if coadministration with moderate or strong CYP3A4 inhibitors is started or continued during study intervention treatment – for more information, see Section 6. Study Intervention and Concomitant Therapy of the study protocol.
- Treatment B: matched placebo twice daily for 7 days (n = 60).

The study includes a Screening Period (Day -1 to Day 1), a Treatment Period (Day 1 to Day 7/8 [depending on timing of first dose]), and a Follow-up Period (Day 8/9 to Day 35 [±3]). In general, the total study duration for each participant is 35 (±3) days.

Study interventions is administered orally. Study intervention administration should start as soon as possible, but no later than 4 hours after randomization. Randomization must occur within a window of 72 hours of RSV symptom onset.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic overview of the study



More information about the study can be found in the protocol, Section 4.1 Overall Design.

2. STATISTICAL HYPOTHESES

As this is an exploratory, hypothesis-generating study, no formal statistical testing was planned.

For exploratory purposes, the primary hypothesis of this study is that rilematovir reduces the time to resolution of the RSV LRTD symptoms compared to placebo, as assessed by a PRO measure (RiiQ^{TM} Symptom Scale) in adult outpatients with at least moderate RSV disease and who are at high risk for RSV disease related progression.

3. SAMPLE SIZE DETERMINATION

The study aims to enroll approximately 180 participants in a 2:1 ratio to rilematovir 250 mg twice daily (approximately 120 participants) and placebo (approximately 60 participants).

The sample size calculation is based on the primary efficacy endpoint, which is the time to resolution of RSV LRTD symptoms from initiation of treatment to Day 35 in the Intent-to-Treat infected (ITT-i) analysis set.

With a sample size of 180 participants, there is an 80% probability to demonstrate a reduction of at least 20% in the primary efficacy endpoint when the true effect is 30%. As further guidance

for the sample size of this study, the power to detect a treatment difference for the primary efficacy endpoint is also calculated.

An accelerated failure time (AFT) model with underlying log-normal distribution for the time to resolution is assumed with a median in a placebo arm of 14 days and a scale parameter of 0.8 (as observed in Study 53718678RSV2004). Using the Gehan-Wilcoxon test to analyze the data and based on the assumptions that the time to recovery is improved by 30%, that approximately 10% of the total enrolled participants may not be centrally confirmed RSV positive, and that 5% of patients may drop out of the study early before reaching resolution of their RSV LRTD symptoms, a sample size of 180 participants (randomized in a 2:1 ratio to rilematovir 250 mg twice daily and placebo) will have an estimated power of 80% as based on 10,000 simulations using a 10% 2-sided significance level. The power was estimated as the number of simulated studies where the 2-sided p-value from the Gehan-Wilcoxon test was <0.1 out of the 10,000 simulated datasets.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Patient profiles will be produced for all participants who signed the main Informed Consent Form (ICF) and who were randomized in the study, regardless of being treated or not.

In addition, patient profiles including limited information: ie, demographic and safety data, will also be produced for participants who signed the pre-screening (diagnostic) ICF and experienced a study procedure-related Adverse Event (AE), even if participant was not randomized.

5. STATISTICAL ANALYSES

5.1. General Considerations

No efficacy and safety summary analyses will be performed and only listings will be generated for each participant.

Clinical data will be reported through patient profiles, which will be produced using SAS® version 9.4 (or higher).

5.1.1. Phase Definitions

Not applicable

5.1.2. Baseline

Not applicable

5.1.3. Relative Day

Study Day 1 is the reference day and defined as the date of first dose of study intervention intake (there is no ‘Day 0’). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

- The relative day for visits **before Day 1** will be defined as:

Relative day = visit date – reference date

- The relative day for visits **on or after Day 1** will be defined as:

Relative day = visit date – reference date+1

5.1.4. Visit Windows

All values collected for the parameters listed below will be considered based on their actual date and time.

5.1.5. Data Handling Rules for RSV RNA Viral Load

For reporting purposes, the $\log_{10}$ qRT-PCR viral load will be imputed with the midpoint on the log scale between the limit of detection (LOD) and lower limit of quantification (LLOQ) of the RSV qRT-PCR assay when the result is 'target detected' (TD) but non-quantifiable.

- For the RSV-A qRT-PCR assay, the LOD is 620 copies/mL and the LLOQ is 1000 copies/mL, a result that is TD will be imputed with 2.90 $\log_{10}$ copies/mL.
- For the RSV-B qRT-PCR assay, the LOD is 80 copies/mL and the LLOQ is 250 copies/mL, a result that is TD will be imputed with 2.15 $\log_{10}$ copies/mL.

When the result is 'target not detected' (TND) (i.e., below the LOD), for both RSV A and RSV B the value of TND will be imputed with 0 $\log_{10}$ copies/mL.

For the overall reporting of viral load, all the viral load results of the RSV type with which the participant has been infected will be used.

In case of co-infection with both subtypes RSV A and B, the rules below will be applied for the overall analyses of viral load from the time the co-infection is detected (i.e., result of TD or >LLOQ):

- In case of two quantifiable results: the $\log_{10}$ of the sum of the RSV A and RSV B results in copies/mL will be used.
- In case of a quantifiable result and a TD/TND result: use the imputed TD/TND on the copies/mL scale value and then use the $\log_{10}$ of the sum of the imputed value and the quantifiable result.
- In case of two TD results, or one TD and one TND result: use the imputed TD/TND on the copies/mL scale values and then use the $\log_{10}$ of the sum of the imputed values.
- In case of two TND results: impute as 0 $\log_{10}$.

5.2. Participant Dispositions

Table 3 presents a list of the disposition information variables that will be reported in the patient profiles. The randomization listing will be included as appendix in the CSR.

Table 3: Disposition information

Variables
Date of signature on ICF: ie, main and diagnostic (if applicable) ICF
Eligibility criteria met (no, yes) If no, criterion
Date and time of randomization
Stratification factors at randomization: • High risk for RSV-related disease progression (actual values: combination of participant age and risk factors for severe RSV: ie, Asthma, COPD and/or CHF, reported at screening in the electronic Case Report Form [eCRF]): - < 65 years of age with underlying high-risk comorbid cardiopulmonary conditions - ≥ 65 years of age without underlying comorbid cardiopulmonary conditions - ≥ 65 years of age with underlying high-risk comorbid cardiopulmonary conditions • Time since symptom onset (as entered into the Interactive Web Response System [IWRS]): - ≤ 48 hours - > 48-72 hours
Treatment group: ie, Placebo/JNJ-53718678
Date and time of first study drug administration and dose: ie, 250 mg OR 125 mg
Date (study day) and time of last study drug administration and dose: ie, 250 mg OR 125 mg
Completed the study treatment: completed (date) OR discontinued (date) If discontinued, reason for treatment discontinuation
Completed the study: completed (date) OR discontinued (date) If discontinued, reason for study discontinuation

5.3. Primary Endpoint Analysis

The primary efficacy variables presented in the patient profiles are listed below.

Table 4: Efficacy primary endpoint

Variables
Plot over time: days since first drug intake – all collected values will be displayed
Individual RSV LRTD symptom scores (defined in Table 5) will be plotted over time using the ordinal variable grading symptom: "None", "Mild", "Moderate", "Severe", for the y-axis. It will include Pre-existing symptom scores (color code: "score before the RSV infection") and RiiQ™ RSV LRTD symptom scores.

Table 5: Clinical Course Parameters

Measurement	Formula
Symptoms (Pre-existing and RiiQ™ Symptom Scale)	
RiiQ™ symptom score	RiiQ™ Symptom Scale is a 13-items questionnaire (see Appendix 12) which ranges from 'None' (score=0; symptom free) to 'Severe' (score=3; severe symptoms). Arithmetic mean of the 13 items will be calculated if at least 9 out of 13 items are available, otherwise it will be set to missing.
Pre-existing symptom	Pre-existing symptom questionnaire is a 13-items questionnaire (see Appendix 11) which ranges from 'None' (score=0; symptom free)

Table 5: Clinical Course Parameters

Measurement	Formula
Symptoms (Pre-existing and RiiQ™ Symptom Scale)	
questionnaire	to 'Severe' (score=3; severe symptoms).
Pre-existing & RiiQ™ RSV LRTD symptom score	Individual scores of the following LRTD items: cough, wheezing, coughing up phlegm (sputum) and short of breath will be used. If not available, it will be set to missing.
RiiQ™ URTD symptom score	Arithmetic mean of the following 2 URTD items (nasal congestion, sore throat) will be calculated if at least 1 out of 2 items are available, otherwise it will be set to missing.
RiiQ™ LRTD symptom score	Arithmetic mean of the following 4 LRTD items (cough, wheezing, short of breath, coughing up phlegm [sputum]) will be calculated if at least 3 out of 4 items are available, otherwise it will be set to missing.
RiiQ™ body/systemic symptom score	Arithmetic mean of the following 7 body/systemic items (headache, feeling feverish, body aches and pains, fatigue, neck pain, interrupted sleep, loss of appetite) will be calculated if at least 4 out of 7 items are available, otherwise it will be set to missing.

5.4. Secondary Endpoint(s) Analysis

The secondary efficacy variables presented in the patient profiles are listed below.

Table 6: Efficacy secondary endpoint

Variables
Pulmonary and extrapulmonary complications will be reported as AE, see Section 5.6.2.
MRUs: new antibiotic use, or new or increased use in bronchodilator/nebulizer, systemic corticosteroids, or home oxygen supplementation will be reported as concomitant medications and oxygen supplementation, see Appendix 5.
Plot over time: days since first drug intake – all collected values will be displayed
MRUs: medical encounter will be plotted based on start/end dates and type of medical encounter information available in the "Medical Encounters" and "hospitalization (Inpatient)" eCRF pages.
RiiQ™ symptom score over time for (defined in Table 5): • all (13) items • the upper respiratory tract disease (URTD) symptoms, • the lower respiratory tract disease (LRTD) symptoms, • the body/systemic symptoms
Log_{10} RSV RNA viral load actual values (log_{10} copies/mL) as measured with qRT-PCR in nasal swab samples over time. In case of co-infection (RSV A and B), plot will include one line per RSV type and combined RSV A and B). Plot including color code for RSV subtype: ie, RSV A, RSV B and RSV A and B

PGI-S, PGI-C, return to usual health/activities, EQ-5D-5L and RiiQ™ Impact Scales will not be reported in the patient profiles. No time-to-variables will be derived.

5.5. Exploratory Endpoint(s) Analysis

No exploratory efficacy variables other than those included in the secondary endpoints will be reported in the patient profiles.

5.6. Safety Analyses

5.6.1. Extent of Exposure

Not applicable

5.6.2. Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Table 7 presents a list of the safety variables linked to AE that will be reported in the patient profiles.

Table 7: Adverse events

Variables
Information to be provided for each adverse event sorted by start date
• Preferred term/System organ class • Complication related to the RSV infection: (no, yes) If yes, type and subtype of complication: - pulmonary complication: respiratory failure, etc; - extrapulmonary complication: cardiovascular and cerebrovascular disease, etc • Onset: (start date [study day] and time) • End date/time (study day) / ongoing • Toxicity grade • Seriousness criteria: ie, Death, Life threatening, Prolonged/ required hospitalization, Significant disability, Congenital anomaly or birth defect, Other medically important event • Action taken with study treatment and other action taken (if applicable) • Concomitant or additional therapy: ie, no, yes, unknown • Relationship to study treatment: ie, not related, related, not applicable • Outcome: ie, fatal, not recovered or not resolved, recovered or resolved, recovered or resolved with sequelae, recovering or resolving, unknown
Plot over time: days since first drug intake – all collected values will be displayed
Occurrence of AEs will be plotted over time including Preferred term and color code to identify any Serious Adverse Event.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

The laboratory abnormalities will be determined according to the Division of Microbiology and Infectious Diseases (DMID) adult toxicity tables (see Appendix 10). In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used.

Table 8 presents the list of clinical laboratory tests that will be reported in the patient profiles.

Table 8: Clinical laboratory tests

Variables
Plot over time: days since first drug intake – all collected values will be displayed
• Clinical hematology tests • Clinical chemistry tests especially eGFR, creatinine, liver function tests (AST, ALT, direct/indirect/total bilirubin and ALP), cardiac electrolytes: ie, sodium, potassium, magnesium, calcium, chloride, phosphorus) Actual values with toxicity/abnormality flagged will be plotted over time

Local laboratory results will not be displayed.

5.6.3.2. Vital Signs and Physical Examination Findings

The vital signs abnormalities will be defined as indicated in Table 9.

Table 9: Clinically important abnormalities in vital signs

Vital Sign	Abnormality Code	Criteria
Systolic blood pressure	Abnormally low	≤ 90 mmHg
	Grade 1 or mild	> 140 mmHg - < 160 mmHg
	Grade 2 or moderate	≥ 160 mmHg - < 180 mmHg
	Grade 3 or severe	≥ 180 mmHg
Diastolic blood pressure	Abnormally low	≤ 50 mmHg
	Grade 1 or mild	> 90 mmHg - < 100 mmHg
	Grade 2 or moderate	≥ 100 mmHg - < 110 mmHg
	Grade 3 or severe	≥ 110 mmHg
Respiratory rate	Grade 1 or mild	17-20 breaths per minute
	Grade 2 or moderate	21-25 breaths per minute
	Grade 3 or severe	> 25 breaths per minute
	Grade 4 or potentially life threatening	intubation
Oxygen Saturation	Abnormally low	< 95%
Temperature (oral, axillary)	Abnormally high	> 38.0 °C
Pulse/Heart Rate	Abnormally low	≤ 45 bpm
	Abnormally high	≥ 120 bpm

Table 10 presents a list of vital signs that will be reported in the patient profiles.

Table 10: Vital signs

Variables
Plot over time: days since first drug intake – all collected values will be displayed
Vital signs parameters including systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, oxygen saturation (SpO_2), weight: • Actual values with abnormality flagged will be plotted over time

5.6.3.3. Electrocardiogram

The ECG abnormalities will be defined as indicated in Table 11.

Table 11: ECG abnormalities

ECG parameter	Abnormality Code	Criteria
Abnormalities on actual values		
Heart Rate	Abnormally low	≤ 45 bpm
	Abnormally high	≥ 120 bpm
PR	Abnormally high	≥ 210 ms
QRS	Abnormally high	≥ 120 ms
$QT_{corrected}$	Borderline prolonged QT	450 ms < QTc ≤ 480 ms
	Prolonged QT	480 ms < QTc ≤ 500 ms
	Pathologically prolonged QT	QTc > 500 ms
Abnormalities on changes from baseline (ΔQTc)		
$QT_{corrected}$	Normal QTc change	ΔQTc ≤ 30 ms
	Borderline QTc change	30 ms ≤ ΔQTc ≤ 60 ms
	Abnormally high QTc change	ΔQTc > 60 ms

Table 12 presents the list of ECG parameters that will be reported in the patient profiles.

Table 12: ECG parameters

Variables
Plot over time: days since first drug intake – all collected values will be displayed
For ECG parameters including PR, QRS, QT, QTc intervals, and heart rate • Actual values with abnormality flagged will be plotted over time
List
ECG overall interpretation per visit: ie, Normal, Abnormal (specify and clinically significant), Not evaluable

5.7. Other Analyses

5.7.1. Virology

Viral Strain Typing

The RSV subtype is determined at baseline using the RSV-A/B RT-qPCR assay performed in the central laboratory.

Viral Sequencing

Viral resistance will be evaluated by next-generation sequencing (NGS) of the RSV Fusion (F) gene using a read frequency cut-off of 3%.

Baseline samples from all participants will be sequenced to identify pre-existing genetic variations in the F gene. Post-baseline sequencing will be performed on the last evaluable on-treatment sample and/or during follow-up for all participants (if viral load is high enough) to identify emerging amino acid substitutions in the F gene. Additional post-baseline sequencing can be performed on request of the sponsor virologist.

Given the small number of participants, the viral sequencing data will be generated, but no formal analysis will be planned.

5.8. Interim Analyses

Not applicable.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
AFT	accelerated failure time
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
AUC	area under the curve
BL	Baseline
BMI	body mass index
bpm	beats per minute
CHF	congestive heart failure
Cmax	maximum concentration
COPD	chronic obstructive pulmonary disease
CSR	Clinical Study Report
CSS	Clinician Symptom Score
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
eCRF	electronic case report form
EPR-3	Expert panel report 3
ePRO	Electronic Patient Report Outcome
EQ-5D-5L	5 level EuroQol© 5 Dimension (EQ-5D-5L) questionnaire
F	Fusion
GOLD	Global initiative for chronic obstructive lung disease
HRQOL	Health-Related Quality of Life
ICF	Informed consent form
ICU	intensive care unit
ITT-i	Intent-to-Treat infected
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOD	limit of detection
LRTD	lower respiratory tract disease
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliters
mmHg	millimeters of mercury
MRU	medical resource utilization
ms	milliseconds
NAEPP	National asthma education and prevention program
NGS	next-generation sequencing
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of RSV Severity
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamics

qRT-PCR	quantitative reverse transcription polymerase chain reaction
QT	QT interval
QTc	corrected QT
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RiiQ™	Respiratory Infection Intensity and Impact Questionnaire
RNA	ribonucleic acid
RSV	Respiratory Syncytial Virus
RSV-A	RSV-A Long strain (GenBank Accession number AY911262)
RSV-B	RSV-B strain 9320 (GenBank Accession number AY353550)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SpO_2	peripheral capillary oxygen saturation
TD	target detected
TE	intervention-emergent
Tmax	time to maximum concentration
TND	target not detected
URTD	upper respiratory tract disease
VL	viral load
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Due to the early termination of the PRIMROSE study and that data of only 5 randomized participants were collected, it was decided to simplify and to reduce the statistical outputs to individual patient profiles. For the PRIMROSE Biosensor substudy, no statistical outputs will be produced as no participants were enrolled in the substudy and therefore no data were collected.

6.3. Appendix 3 Demographics and Baseline Characteristics

Table 13 presents the list of demographic variables that will be reported in the patient profiles.

Table 13: Demographic variables

Variables
Age (years)
Age group: <65 years and ≥65
Weight (kg)
Height at baseline (cm)
Body Mass Index at baseline (BMI) (kg/m2) = weight (kg)/(height (m))^2
Sex: ie, male, female, unknown, undifferentiated
Race: ie, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported, Unknown
Ethnicity: ie, Hispanic or Latino, Not Hispanic or Latino, Not Reported
Country

Table 14 presents the list of baseline and RSV disease characteristics that will be reported in the patient profiles.

Table 14: Baseline and RSV disease characteristics

Variables:
Start date and time of first RSV symptoms/signs
Time since symptom onset as reported in the IWRS: ie, ≤48 hours versus >48-72 hours

Presence of risk factors for severe RSV disease with severity:
• Asthma – National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-3 (EPR-3) Classification of Asthma Severity & Control
  ○ Class 1: Intermittent
  ○ Class 2: Mild
  ○ Class 3: Moderate
  ○ Class 4: Severe
• COPD – Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages for COPD grading
  ○ Class 1: Mild
  ○ Class 2: Moderate
  ○ Class 3: Severe
  ○ Class 4: Very severe
• CHF - New York Heart Association classification of chronic heart failure
  ○ Class 1: No limitation of physical activity
  ○ Class 2: Slight limitation of physical activity
  ○ Class 3: Marked limitation of physical activity
  ○ Class 4: Unable to carry on any physical activity without discomfort

RSV Viral Load (log_{10} copies/ml) overall RSV Viral Load (log_{10} copies/ml) by RSV Subtype (RSV A, RSV B, RSV A+B)
Oxygen saturation at screening (%) Condition of oxygen saturation measurement: ie, supplemental oxygen, room air Is the value similar to pre-RSV infection (no, yes)
Known pre-RSV SpO_2 < 92% (no, yes) If yes, reason: • Pulmonary dysplasia • Other - specify
Received aerosolized or oral ribavirin in the past 6 months prior to Screening (no, yes, unknown)
Received IV immunoglobulin in the past 6 months prior to Screening (no, yes, unknown)

6.3.1. Presence of other respiratory viruses or bacteria

Table 15 presents the list of other respiratory infections that will be reported in the patient profiles.

Table 15: Presence of other respiratory viruses or bacteria

Variables:
Presence of other respiratory viral infection (no, yes) If yes, type of virus
Presence of other respiratory bacterial infection (no, yes) If yes, type of bacteria

6.4. Appendix 4 Protocol Deviations

Protocol deviations will not be reported in the patient profiles. The listing of subjects with major protocol deviations will be included as appendix in the CSR.

6.5. Appendix 5 Prior and Concomitant Medications

Medications taken from the date when the main study ICF is signed through the end of study and pre-disease use: ie, 1 week prior to RSV symptoms for bronchodilator, nebulizer, and systemic or inhaled corticosteroids will be reported.

In the patient profiles concomitant therapy will be displayed by indication:

- Adverse Event
- Medical History
- Prophylaxis
- Trial Indication
- Other

Table 16 presents the list of the concomitant medications and oxygen supplementation variables that will be reported in the patient profiles.

Table 16: Concomitant medications and oxygen supplementation

Variables
Sorted by start date
Medication or Therapy preferred term using the World Health Organization-Drug Dictionary (WHO-DD)
Start date (study day) AND end date (study day) OR ongoing
Dose with unit; route AND frequency
If it is an antibiotic (no, yes)
For adverse event and medical history indication: AE or Medical history term
Plot over time: days since first drug intake – all collected values will be displayed
Type of supplemental oxygen administration

6.5.1. Specific Prior Therapy

Use of specific prior RSV therapies (aerosolized or oral ribavirin, IVIG) will be displayed in the baseline characteristics.

6.6. Appendix 6 Medical History

Table 17 presents the list of the medical history variables that will be reported in the patient profiles.

Table 17: Medical history

Variables
Sorted by start date
Preferred term/System organ class
Start date (study day) AND end date (study day) OR ongoing

The family history will not be reported.

6.7. Appendix 7 Intervention Compliance

Table 18: Treatment compliance

Variables
Plot over time: days since first drug intake
Actual daily (AM/PM) study drug administration will be reported on the plot. Any missed dose will be identified by no dot on the plot Dosing regimens: ie, 250 mg and 125 mg, will be identified by a color code

6.8. Appendix 8 Adverse Events of Special Interest

For rilematovir, no AEs are considered of special interest. However, Hepatobiliary effects and Cardiac events potentially related to QT prolongation are AEs which are safety topics of interest, as detailed in Section 8.3.7 Safety Areas of Evaluation of the study protocol. They will be reported in the AEs section.

6.9. Appendix 9 Medications of Special Interest

Not applicable

6.10. Appendix 10 Laboratory Toxicity Grading

The toxicity grade of laboratory abnormalities will be assessed using the criteria specified in the DMID Toxicity Table (see Protocol Appendix 10.7) by the central laboratory.

6.11. Appendix 11 Pre-Existing Symptom Questionnaire

Thinking back to before you had this illness, about a week ago, read each symptom and check the box that best describes how you felt back then:

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j. Wheezing	☐	☐	☐	☐
k. Coughing up phlegm (sputum)	☐	☐	☐	☐
l. Short of breath	☐	☐	☐	☐
m. Loss of appetite	☐	☐	☐	☐

6.12. Appendix 12 Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) Symptom Scale

Please read each of the following questions and select the answer thinking about when you felt the worst in the past [X] hours.

1. **<u>During the past [X] hours</u>, have you had the following symptoms?**

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j. Wheezing	☐	☐	☐	☐
k. Coughing up phlegm (sputum)	☐	☐	☐	☐
l. Short of breath	☐	☐	☐	☐
m. Loss of appetite	☐	☐	☐	☐

7. REFERENCES

Not applicable